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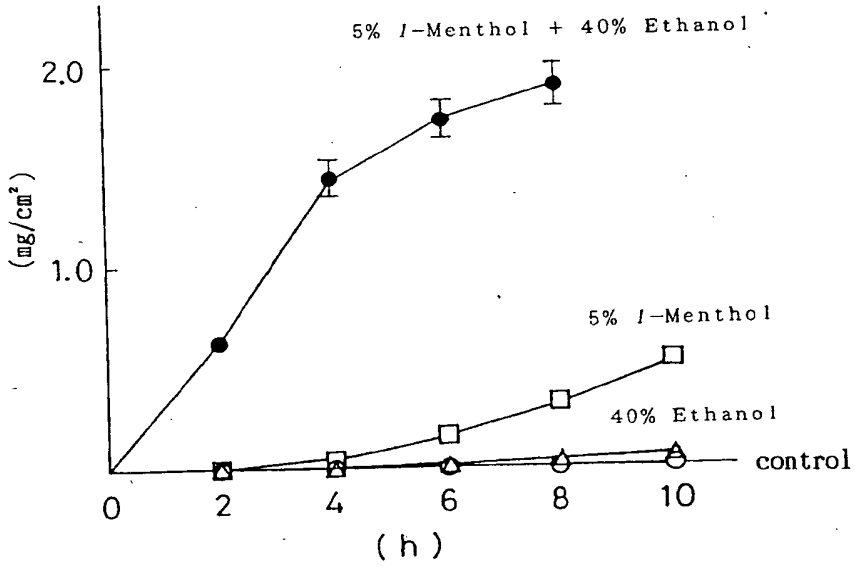
(54) PERCUTANEOUSLY ABSORBABLE COMPOSITION OF NARCOTIC AND NONNARCOTIC ANALGESICS.

(57) A percutaneously absorbable preparation comprising a narcotic analgesic of a low percutaneous absorbability such as morphine hydrochloride or sulfate, a nonnarcotic analgesic such as eptazocine hydrobromide, a percutaneous absorption promoter, and a percutaneous absorption promoter aid.

EP 0 480 054 A1

Fig. 1



Effects of *l*-Menthol and Ethanol on Skin Permeativity of Morphine Hydrochloride

Technical Field

The present invention relates to percutaneously absorbable formations such as analgesics such as morphine, or its salts or bases.

Background Art

Narcotic analgesics such as morphine or its salts and nonnarcotic analgesics such as eptazocine have been orally administered or injected to ease postoperative and cancerous pains.

In the case of such injecting agents, at-home treatment is difficult because of the necessity of administration by a third person, and further medicines having short working times such as morphine are disadvantageously difficult to administer at the time of acute pain because of its increased administration frequency.

Oral agents, which have been developed for the purpose of simplification of administration and use, overcame some disadvantages of the injecting agents, but are not so much improved in working time, in which the migrating property and retentivity of the formations in digestive organs are difficult to control even by pharmaceutical designs for gradual release, and the persistency has its limit.

Further, many cancerated patients in the last stage can not have oral administration of analgesics because of vomiting and nausea which are the side effects of carcinostatic substances.

On the other hand, skin applying formations have expectable persistency of medicinal effect for about 24 hours to 1 week by one administration, and are applicable to patients impossible of oral administration.

In general, medicines have low percutaneous absorbability, and it is the same with analgesics including morphine and its salts.

The main barrier to percutaneous absorption of medicines resides in a horny layer, and various accelerators have been developed as the accelerators were considered to increase the percutaneous absorbability to the lipids of the horny layer. However, the medicine permeability of the epidermis other than the horny layer becomes the barrier in simple absorption accelerators acting on the horny layer and combinations thereof, so that very excellent accelerators have not been developed yet.

In view of the disadvantages of the prior arts, as a result of the earnest studies on utilization of analgesics such as morphine, which were used only as injecting agents and oral agents in the past, for percutaneously absorbable type external agents such as ointment, cream, tape dressing, plaster dressing, patch dressing, and pap dressing (wet dressing), the present inventors have found and attained this invention.

Disclosure of the Invention

The present invention can provide a percutaneously absorbable formation by dissolving a percutaneously absorbable composition of narcotic or nonnarcotic analgesics into a base agent formed of a percutaneous absorption accelerator consisting of a terpene and/or an essential oil and a percutaneous absorption accelerating assistant consisting of a lower alcohol having 1-5 carbon atoms.

As the narcotic analgesics used in the present invention, morphine hydrochloride, ethylmorphine hydrochloride, morphine sulfate, cocaine hydrochloride, pethidine hydrochloride, codeine phosphate, dihydrocodeine phosphate, fentanyl citrate, sufentanil, meperidine hydrochloride and the like are used. As the nonnarcotic analgesics, eptazocine hydrobromide, buprenorphine hydrochloride, butorphanol tartrate, or other salts are used. These analgesics may be constituted by basic ones.

As the percutaneous absorption accelerators, hydrocarbon monoterpenes such as limonene, monoterpene alcohols such as l-menthol, terpineol and borneol, monoterpene aldehydes such as citral, monoterpene ketones such as ionone, other monoterpenes such as cineole, or essential oils containing monoterpenes such as mentha oil, peppermint oil, and eucalyptus oil are used.

As the percutaneous absorption accelerating assistants, lower alcohols having 1-5 carbon atoms such as methyl alcohol, ethyl alcohol, propyl alcohol, butyl alcohol, amyl alcohol, isopropyl alcohol and the like are used.

The blending quantities are varied depending on the kinds of the medicines used, but the percutaneous absorption accelerator is preferably used in a ratio of 1-20 wt.% and the percutaneous absorption accelerating assistant in a ratio of 10-60 wt.%.

As other percutaneous absorption accelerators, alcohols having 8-22 carbon atoms, fatty acids having 8-22 carbon atoms, fatty acid methyl, ethyl, vinyl, n-propyl, isopropyl, propylene, n-butyl, isobutyl and buthylene esters having 8-22 carbon atoms, n-alkylpyrrolidones having 1-16 carbon atoms and/or mixtures

thereof may be added.

Further, as other percutaneous absorption accelerating assistants, water, lower glycols having 2-20 carbon atoms such as glycerol and propylene glycol, lower ketones having 2-5 carbon atoms, or aldehyde may be added.

Brief Description of the Drawings

Figs. 1-11 are graphs showing the changes on standing of absorption quantities of medicines through the skin with various kinds and quantities of medicines, percutaneous absorption accelerators, and percutaneous absorption accelerating assistants related to the formations according to the examples of the present invention and the formations of comparative examples.

Effect

The percutaneous absorption accelerator in the composition physically removes the barrier ability of the horny layer of the skin and enhances the medicine permeability of the skin.

The percutaneous absorption accelerating assistant increases the solubility of the medicine and also medicine permeability, resulting in a remarkable improvement in absorbability of the medicine as an synergistic effect.

Optimum Conditions to Practice the Invention

The present invention is further illustrated in detail according to following examples.

Example 1

Formulations as shown in Table 1 were prepared, and comparatively examined on the change on standing of skin permeating quantity by means of a skin permeation test method described below.

(Skin permeation test method)

The abdominal extracted skin of a hairless rat (male, body weight 150g, available from Saitama Experimental Animals) was put in a 2-chamber diffusing cell (contact area: 1.0 cm^2) of skin permeation test as held at 37° C, 2.5 ml of a medicine solution is put on the horny layer side, and 2.5 ml of water on the derm side. Ten diffusing cell dermic solutions are sampled on the lapse of time, and the quantities of the medicine permeated through the skin after 2, 4, 6, 8 and 10 hours were measured. The results are as shown in Table 2 and Fig. 1.

Table 1 unit: w%

Sample / Component	This Invention 1	Comparative Example 1	Comparative Example 2	Comparative Example 3
Morphine hydrochloride	1	1	1	1
l-Menthol	5	–	–	5
Ethanol	40	–	40	–
Water	54	99	59	4

Table 2 unit: μg/cm²

Time elapsed	This Invention 1		Comparative Ex. 1		Comparative Ex. 2		Comparative Ex. 3	
	Mean	Deviation	Mean	Deviation	Mean	Deviation	Mean	Deviation
2	629	20.9	1.72	0.25	3.58	0.52	10.2	3.73
4	1436	87.3	3.43	0.01	10.3	1.54	49.3	0.12
6	1732	90.9	6.34	0.23	23.0	5.59	161	10.1
8	1893	111	12.6	1.78	40.6	11.4	321	20.1
10	–	–	17.1	3.19	73.3	15.1	533	20.0

The results showed that the formation having *l*-menthol selected as an absorption accelerator and ethanol as an absorption accelerating assistant has excellent percutaneous absorptivity.

Example 2

To examine the relation of the concentration of morphine hydrochloride with skin permeativity, formations shown in Table 3 were prepared and examined on the basis of the skin permeation test.

Table 3 unit: w%

Component	This Invention 1	2	3
Morphine hydrochloride	1	10	0.01
l-Menthol	5	5	5
Ethanol	40	40	40
Water	54	45	54.99

As shown in Fig. 2 and Table 4, the results showed the medicine is absorbed percutaneously corresponding to the concentration of morphine hydrochloride.

Table 4 unit: μg/cm²

Time elapsed	This Invention 1		This Invention 2		This Invention 3	
	Mean	Deviation	Mean	Deviation	Mean	Deviation
2	629	20.9	6256	213	8.45	0.08
4	1436	87.3	14399	671	17.4	0.34
6	1732	90.9	20323	940	27.7	1.03
8	1893	111	24958	1142	35.0	0.63
10	–	–	28410	1580	40.4	0.88

Example 3

Formulations containing different kinds of percutaneous absorption accelerators were prepared as shown in Table 5, and comparatively examined for percutaneous absorbability of morphine hydrochloride in the same manner as in Example 1.

Table 5 unit: w%

Component	This Invention		
	1	4	5
Morphine hydrochloride	1	1	1
l-Menthol	5	–	–
Terpineol	–	5	–
Peppermint oil	–	–	5
Ethanol	40	40	40
Water	54	54	54

Consequently, as shown in Fig. 3 and Table 6, excellent percutaneous absorbability was shown in every percutaneous absorption accelerator, but particularly the best in terpineol.

Table 6 unit: μg/cm²

Time elapsed	This Invention 1		This Invention 4		This Invention 5	
	Mean	Deviation	Mean	Deviation	Mean	Deviation
2	629	20.9	1046	44.5	854	65.2
4	1436	87.3	2111	107	1766	64.7
6	1732	90.9	3163	226	2283	73.3
8	1893	111	3884	223	2662	93.8
10	–	–	–	–	3087	100

Example 4

To examine the effect of the concentration of ℓ-menthol on skin permeability of morphine hydrochloride from ℓ-menthol-ethanol-water system, formations as shown in Table 7 were prepared and examined for percutaneous absorbability.

Table 7 unit: w%

Sample	This Invention			Comparative Ex.	
Component	6	1	7	4	5
Morphine hydrochloride	1	1	1	1	1
l-Menthol	2.5	5	10	1	0.1
Ethanol	40	40	40	40	40
Water	56.4	54	49	58	58.9

As shown in Fig. 4 and Table 8, the results showed that skin permeativity is excellent when the concentration of menthol is 2.5 w% or more.

Table 8 unit: $\mu g/cm^2$

Time elapsed	This Invention 1		This Invention 6		This Invention 7		Comp.Ex. 4		Comp. Ex. 5	
	Mean	Deviation	Mean	Deviation	Mean	Deviation	Mean	Deviation	Mean	Deviation
2	629	20.9	292	39.8	524	67.1	0.0	0.0	0.0	0.0
4	1436	87.3	876	47.4	1164	88.0	18.4	2.77	2.42	0.63
6	1732	90.9	1340	62.4	1665	94.8	83.4	15.5	6.90	1.27
8	1893	111	1717	57.8	2020	65.0	226	40.3	19.0	2.02
10	-	-	2057	71.9	2271	58.3	450	63.4	30.4	2.28

Example 5

To examine the effect of the concentration of ethanol which is a percutaneous absorption accelerating assistant on skin permeativity of morphine hydrochloride from ℓ-menthol-ethanol-watersystem, formations shown in Table 9 were prepared and examined for percutaneous absorbability.

Table 9 unit: w%

Sample	This Invention			Comparative Ex.	
Component	8	1	9	6	7
Morphine hydrochloride	1	1	1	1	1
l-Menthol	5	5	5	5	5
Ethanol	20	40	60	80	94
Water	74	54	34	14	-

As shown in Fig. 5 and Table 10, the results showed that skin permeativity is excellent when the

concentration of ethanol is 20 w% or more and less than 60 w%.

Table 10 unit: μg/cm²

Time elapsed	This Invention 1		This Invention 8		This Invention 9		Comp. Ex. 6		Comp. Ex. 7	
	Mean	Deviation	Mean	Deviation	Mean	Deviation	Mean	Deviation	Mean	Deviation
2	629	20.9	45.0	4.08	15.9	2.0	0.72	0.7	0.76	0.76
4	1436	87.3	182	0.80	251	6.84	6.84	1.02	5.92	4.72
6	1732	90.9	366	18.3	688	33.6	33.6	0.13	25.8	18.6
8	1893	111	570	62.1	1106	226	104	0.29	66.6	46.3
10	-	-	942	87.4	-	-	-	-	-	-

Example 6

To examine the effect of the concentration of isopropyl alcohol (IPA) adapted instead of ethanol on skin permeativity of morphine hydrochloride from l-menthol-alcohol-water system, formations shown in Table 11 were prepared and examined for percutaneous absorbability.

Table 11 unit: w%

Sample	This invention		
Component	10	11	12
Morphine hydrochloride	1	1	1
l-Menthol	5	5	5
IPA	20	40	60
Water	74	54	34

Consequently, as shown in Fig. 6 and Table 12, the skin permeativity was excellent when the concentration of isopropyl alcohol is 20 wt.% or more and less than 60 wt.% similarly to the case of ethanol, and too much high concentration rather aggravated the absorbability.

Table 12 unit: μg/cm²

Time elapsed	This Invention 1		This Invention 10		This Invention 11		This Invention 12	
	Mean	Deviation	Mean	Deviation	Mean	Deviation	Mean	Deviation
2	629	20.9	229	44.4	348	31.8	3.43	2.80
4	1436	87.3	655	94.7	1663	75.3	75.8	13.0
6	1732	90.9	1073	145	2624	68.2	227	32.6
8	1893	111	1546	184	3420	64.1	432	48.5
10	-	-	1922	178	3891	40.4	696	65.6

Example 7

Instead of the water added as the supplement of ethanol of the percutaneous absorption accelerating assistant having an influence on skin permeativity of morphine hydrochloride from ℓ-menthol-alcohol-water system, glycerol was mixed as shown in Table 13, and this was comparatively examined for percutaneous absorbability.

As shown in Fig. 7 and Table 14, the results showed that the percutaneous absorbability similar to the case of water can be held when glycerol is used.

Table 13 unit: w%

Sample / Component	This Invention 1	This Invention 13
Morphine hydrochloride	1	1
l-Menthol	5	5
Ethanol	40	40
Water	54	-
Glycerol	-	54

Table 14 unit: $\mu g/cm^2$

Time elapsed	This Invention 1		This Invention 13	
	Mean	Deviation	Mean	Deviation
2	629	20.9	26.8	8.40
4	1436	87.3	235	76.8
6	1732	90.9	687	163
8	1893	111	1172	169
10	-	-	1568	144

Example 8

To examine the skin permeativities of other medicines to ℓ-menthol-ethanol-water system, formations using fentanyl citrate (FTC), eptazocine hydrobromide (ETH), cocaine hydrochloride (CCH), and morphine hydrochloride were prepared and examined for percutaneous absorbability.

Table 15 unit: w%

Sample / Component	This Invention 1	14	15	16
Morphine hydrochloride	1	-	-	-
FTC	-	1	-	-
ETH	-	-	1	-
CCH	-	-	-	1
l-Menthol	5	5	5	5
Ethanol	40	40	40	40
Water	54	54	54	54

As shown in Fig. 8 and Table 16, the results showed that every formation is excellent in skin permeativity in the ℓ-menthol-ethanol-water system.

Table 16 unit: μg/cm^2

Time elapsed	This Invention 1		This Invention 14		This Invention 15		This Invention 16	
	Mean	Deviation	Mean	Deviation	Mean	Deviation	Mean	Deviation
2	629	20.9	570	19.5	586	61.7	495	11.2
4	1436	87.3	1539	56.4	1729	87.8	1353	13.7
6	1732	90.9	2274	66.9	2349	57.9	2018	40.4
8	1893	111	3086	122	3095	52.0	2549	14.3
10	-	-	3692	187	3691	50.7	2694	38.1

Example 9

To examine the effect of different concentration of ℓ-menthol on skin permeativity of eptazocine hydrobromide from ℓ-menthol-ethanol-water system, formations as shown in Table 17 were prepared and examined for percutaneous absorbability.

Table 17 unit: w%

Component \ Sample	This Invention 17	This Invention 18	This Invention 15
E.T.H.	1	1	1
l-Menthol	1	2	5
Ethanol	40	40	40
Water	58	57	54

As shown in Fig. 9 and Table 18, the results showed that skin permeativity is excellent when the concentration of menthol is 1.0 wt.% or more.

Table 18 unit: μg/cm^2

Time elapsed	This Invention 17		This Invention 18		This Invention 15	
	Mean	Deviation	Mean	Deviation	Mean	Deviation
2	55.03	67.10	669.7	170.8	586.3	61.70
4	556.3	380.3	1638	117.0	1729	87.77
6	1264	275.4	2063	99.52	2349	57.93
8	1922	223.9	2623	36.51	3095	52.03
10	2407	170.8	3017	44.86	3691	50.61

Example 10

To examine the effect of the concentration of ethanol on skin permeativity of eptazocine hydrobromide from ℓ-menthol-ethanol-water system, formations as shown in Table 19 were prepared and examined for percutaneous absorbability.

Table 19 unit: w%

Sample / Component	This Invention 19	This Invention 20	This Invention 15
E.T.H.	1	1	1
l-Menthol	5	5	5
Ethanol	10	20	40
Water	84	73	54

As shown in Fig. 10 and Table 19, the results showed that skin permeativity is excellent when the concentration of ethanol is 10 wt.% or more.

Table 20 unit: $\mu g/cm^2$

Time elapsed	This Invention 19		This Invention 20		This Invention 15	
	Mean	Deviation	Mean	Deviation	Mean	Deviation
2	9.121	9.592	97.25	14.79	586.3	61.70
4	127.3	78.04	324.6	187.0	1729	87.77
6	393.5	207.5	1138	195.9	2349	57.93
8	755.6	303.4	1599	243.3	3095	52.03
10	1170	276.0	2152	422.4	3691	50.61

Example 11

To examine the effect of concentration of eptazocine hydrobromide on skin permeativity of eptazocine hydrobromide from ℓ-menthol-ethanol-water system, formations as shown in Table 21 were prepared and examined for percutaneous absorbability.

Table 21 unit: w%

Component \ Sample	This Invention 21	This Invention 22	This Invention 15
E.T.H.	0.1	5	1
ℓ-Menthol	5	5	5
Ethanol	40	40	40
Water	54.9	50	54

As shown in Fig. 11 and Table 22, the results showed that skin permeativity is excellent when the concentration of eptazocine bromohydride is 1.0 wt.% or more.

Table 22 unit: μg/cm²

Time elapsed	This Invention 19		This Invention 20		This Invention 15	
	Mean	Deviation	Mean	Deviation	Mean	Deviation
2	53.82	2.934	1418	586.3	586.3	61.70
4	132.2	13.47	8013	328.3	1729	87.77
6	206.1	26.52	14273	549.4	2349	57.93
8	268.2	23.03	19415	103.5	3095	52.03
10	311.0	27.65	23300	913.5	3691	50.61

Industrial Applicability

The percutaneous absorption accelerating formations according to the present invention allow the administration from the skin for medicines which could not be administered from the skin in the past by adapting monoterpenes which were only used as perfumes as percutaneous absorption accelerators and lower alcohols having 1-5 carbon atoms as skin absorption accelerating assistants, and combining them.

As the prevent invention has a constitution for percutaneous absorption, formations having long analgesic effects can be provided.

The formations according to the present invention are suitable for at-home treatment because of their easy recipe, compared with injecting agents and oral agents, and excellent in persistency.

Claims

1. A percutaneously absorbable composition of narcotic or nonnarcotic analgesics which contains a percutaneous absorption accelerator consisting of a terpene and/or an essential oil and a percutaneous absorption accelerating assistant consisting of a lower alcohol having 1-5 carbon atoms, and water or a lower glycol having 2-5 carbon atoms.

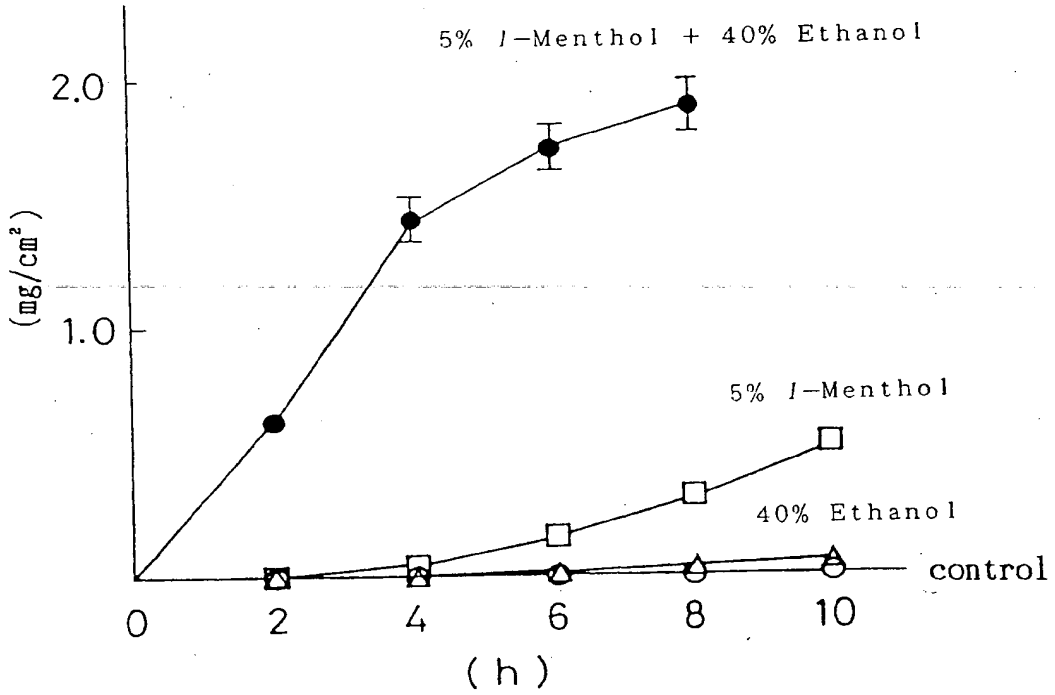
2. A percutaneously absorbable composition according to claim 1 wherein the percutaneous absorption accelerator is a monoterpene such as ℓ-menthol and terpineol, or an essential oil containing a monoterpene such as mentha oil and peppermint oil.

3. A percutaneously absorbable composition according to claim 1 wherein the percutaneous absorption accelerator is used in a ratio of 1-20 wt.% and the percutaneous absorption accelerating assistant in a ratio of 10-60 wt.%.

4. A percutaneously absorbable composition according to claim 1 wherein the percutaneous absorption accelerating assistant is any one of lower alcohols 1-5 carbon atoms of methyl alcohol, ethyl alcohol, propyl alcohol, butyl alcohol, amyl alcohol, and isopropyl alcohol, and combinations of a plurality thereof.

5. A percutaneously absorbable composition according to claim 2 wherein the percutaneous absorption accelerator is used in a ratio of 1-20 wt.% and the percutaneous absorption accelerating assistant in a ratio of 10-60 wt.%.

Fig. 1



Effects of *l*-Menthol and Ethanol on Skin Permeativity of Morphine Hydrochloride

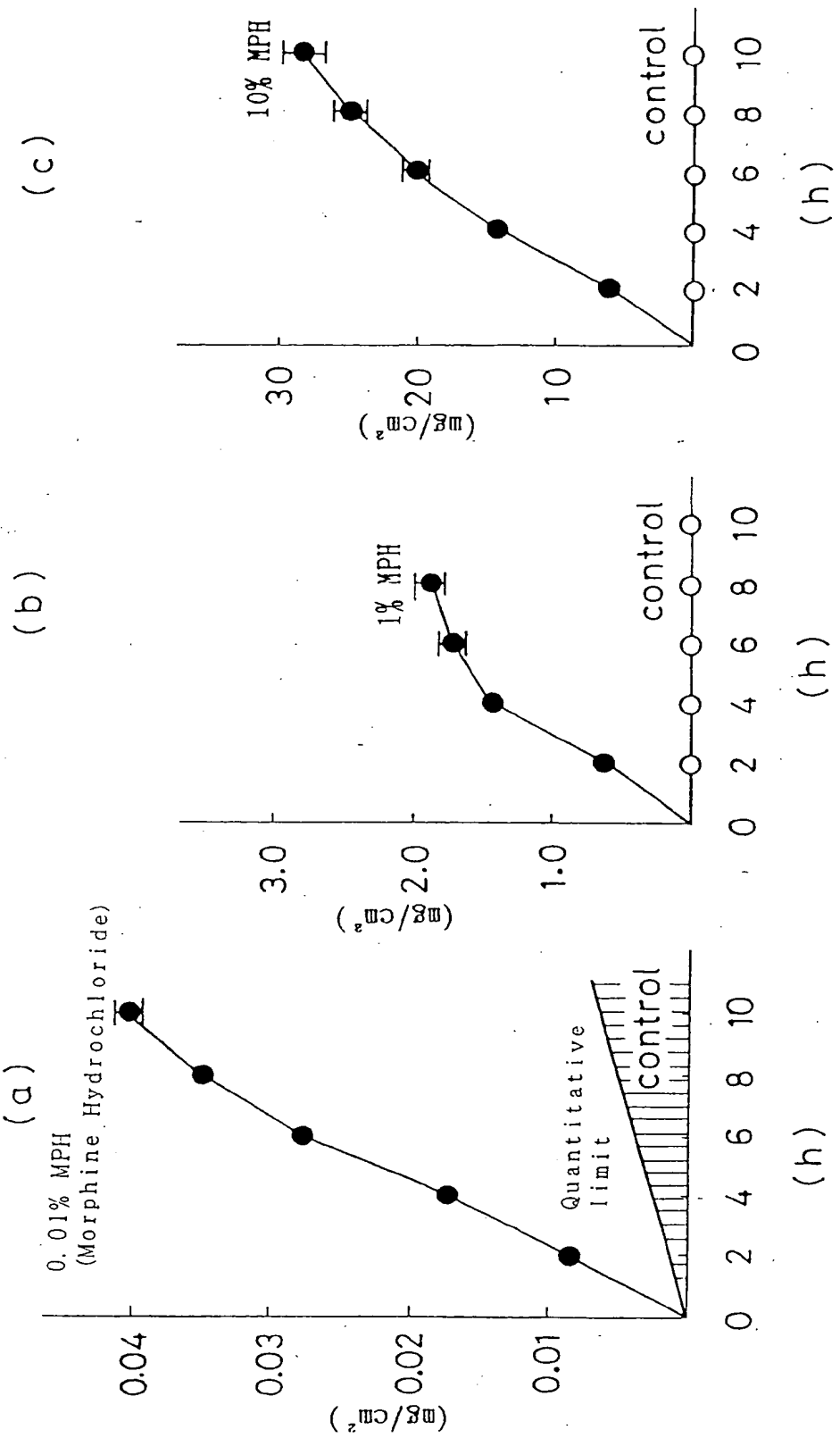
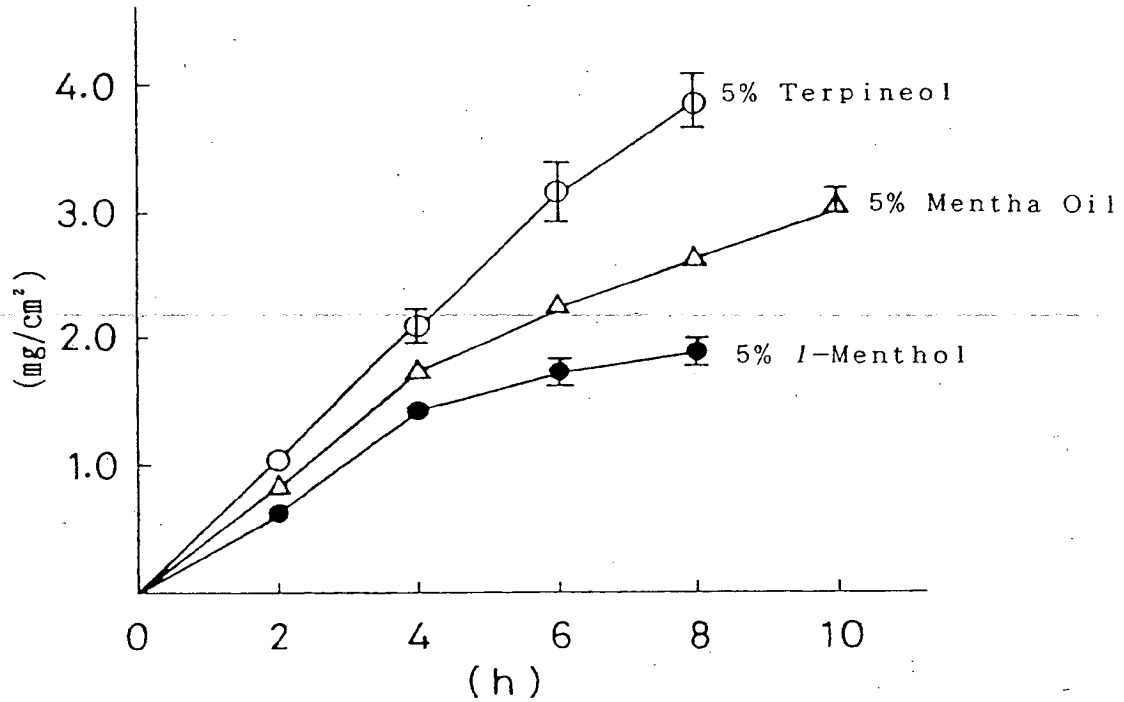


Fig. 2

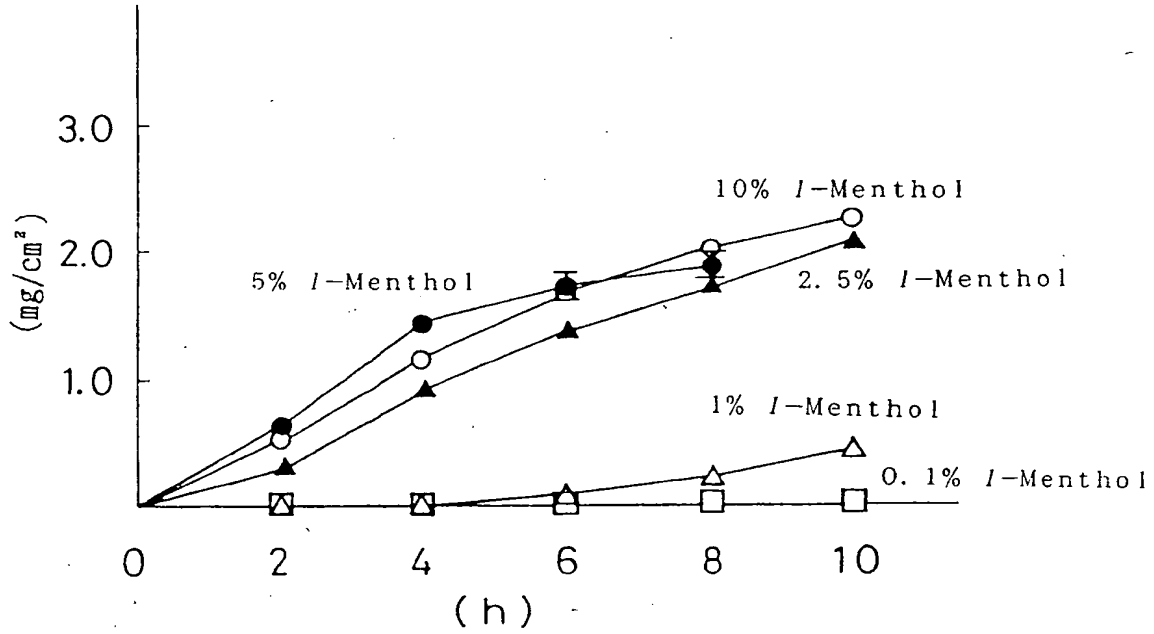
Effects of concentration of Morphine Hydrochloride on skin Permeativity of Morphine Hydrochloride from *l*-Menthol-Water System

Fig. 3



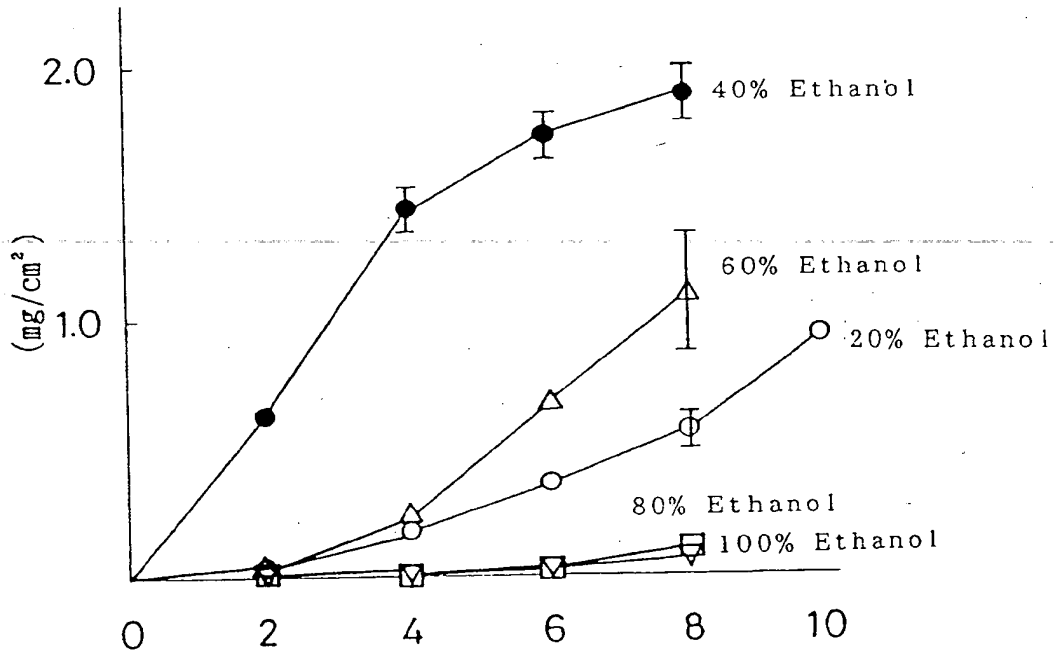
Effects of kinds of Terpenes on Skin Permeativity of Morphine Hydrochloride from Terpene-Etanol-Water System

Fig. 4



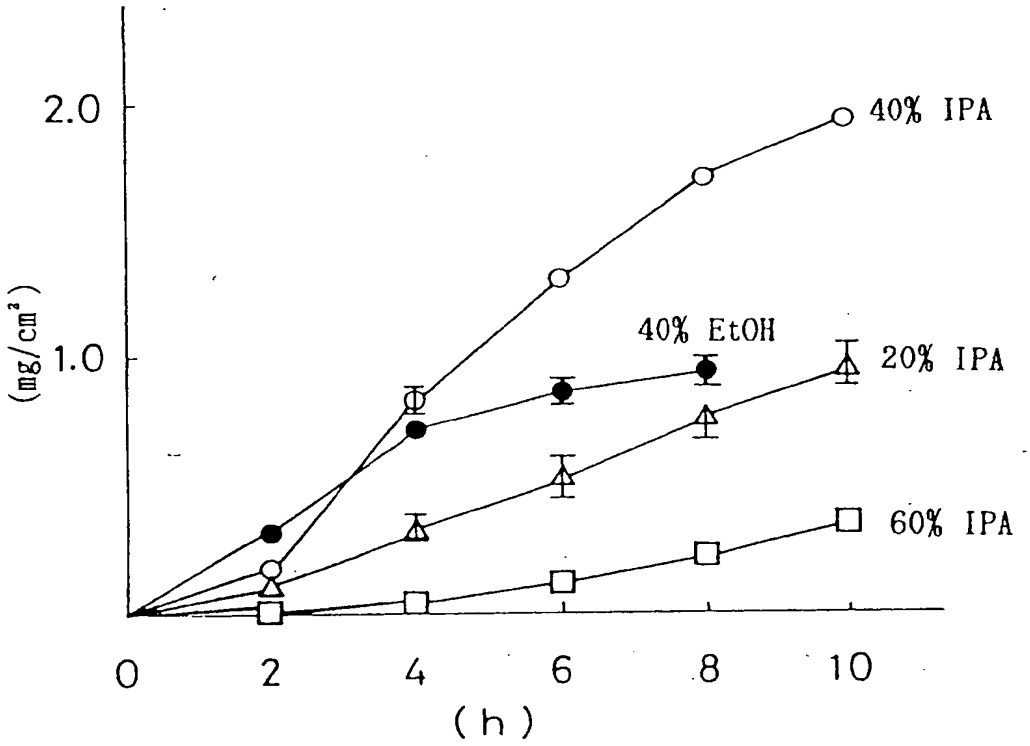
Effect of Concentration of *l*-Menthol on Skin Permeativity of Morphine Hydrochloride from *l*-Menthol-Ethanol-Water System

Fig. 5



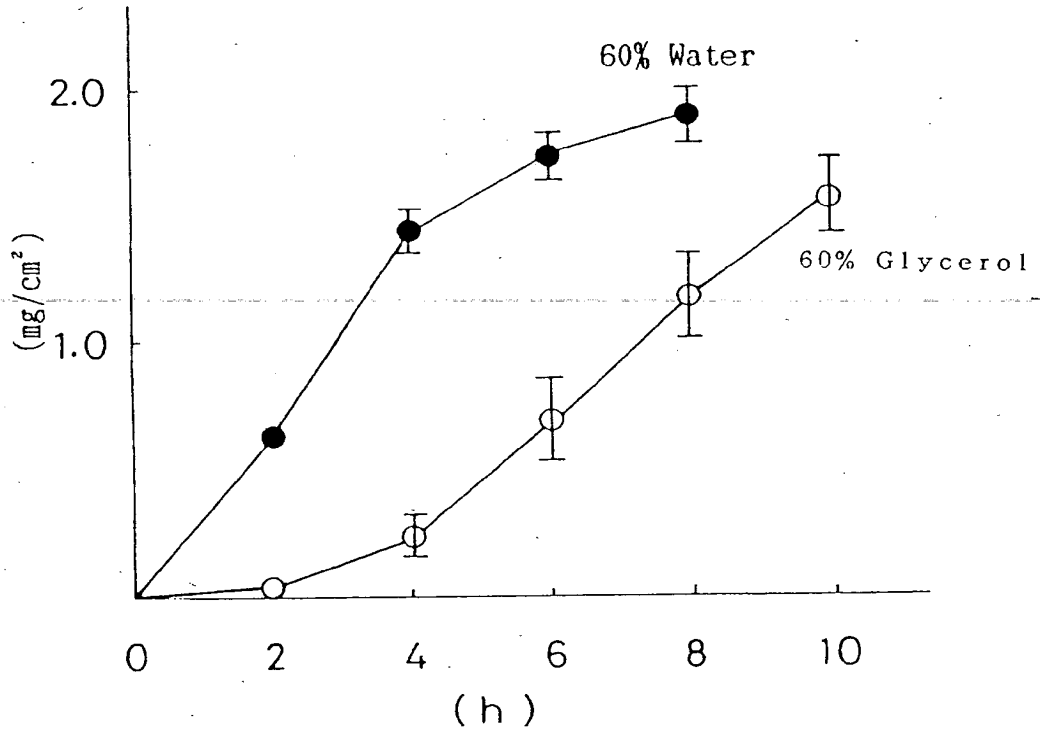
Effect of Concentration of Ethanol on Skin Permeativity of Morphine Hydrochloride from *l*-Menthol-Ethanol-Water System

Fig. 6



Effect of Isopropyl Alcohol (IPA) on Skin Permeativity of Morphine Hydrochloride from *L*-Menthol-Ethanol-Water System

Fig. 7



Comparison of *l*-Menthol-Ethanol-Water-System with *l*-Menthol-Ethanol-Glycerol System on Skin Permeativity of Morphine Hydrochloride

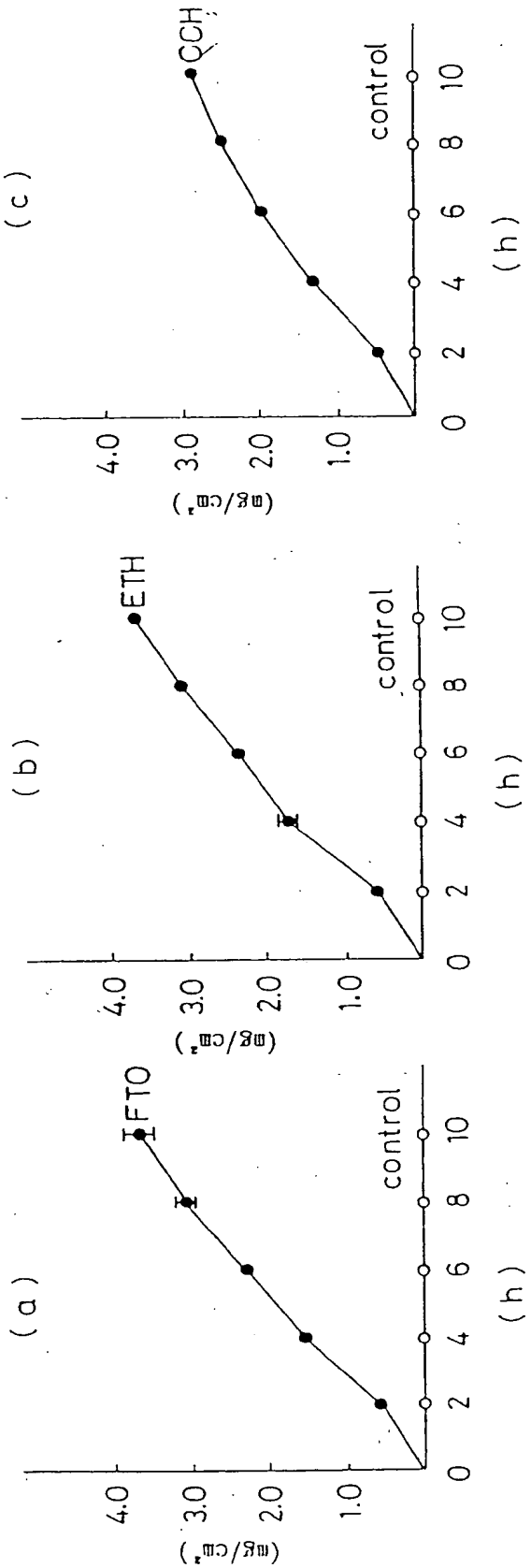


Fig. 8

Skin Permeativities of other Medicines to *l*-Menthol-Ethanol-Water-System

Fig. 9

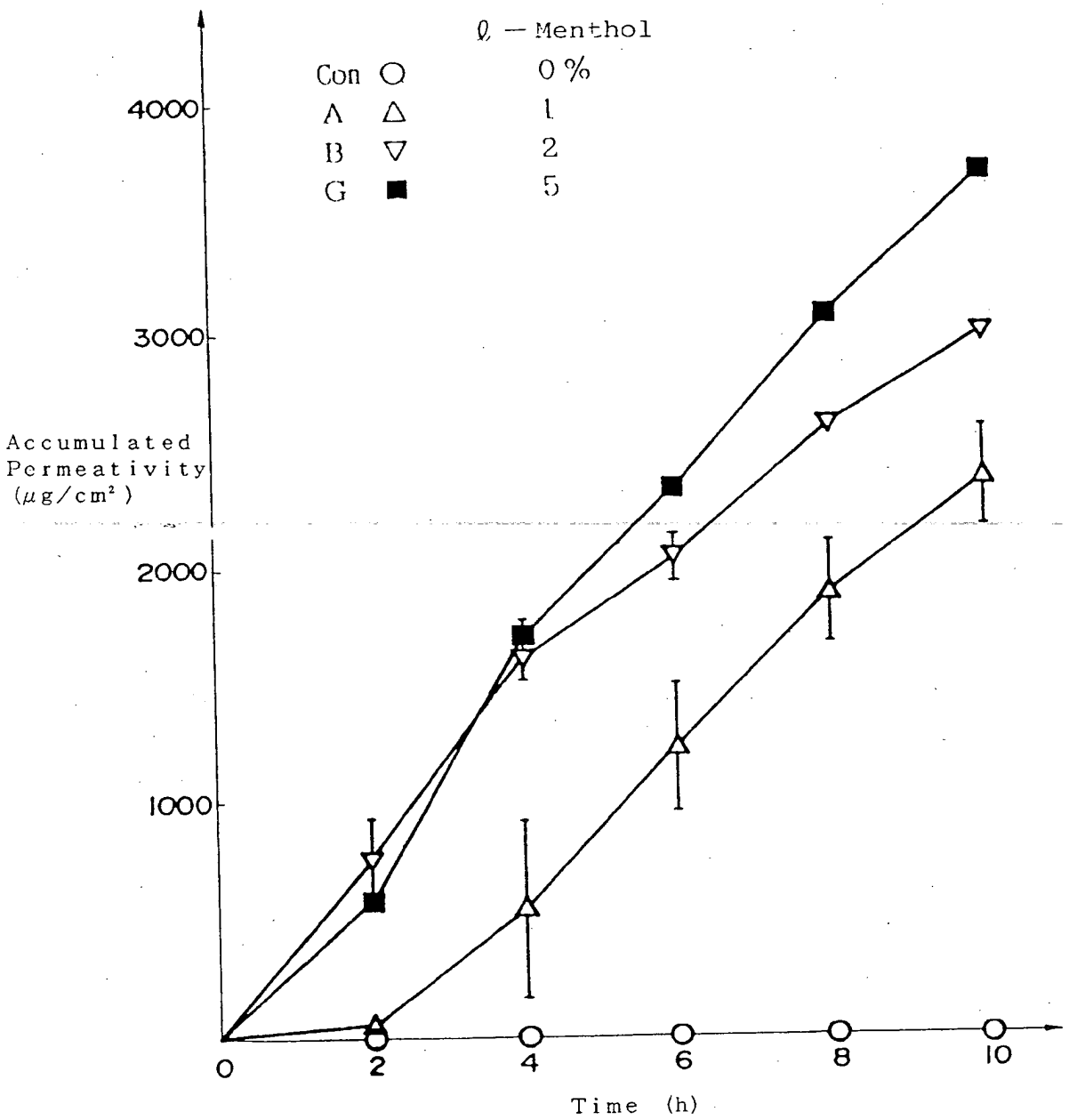


Fig. 10

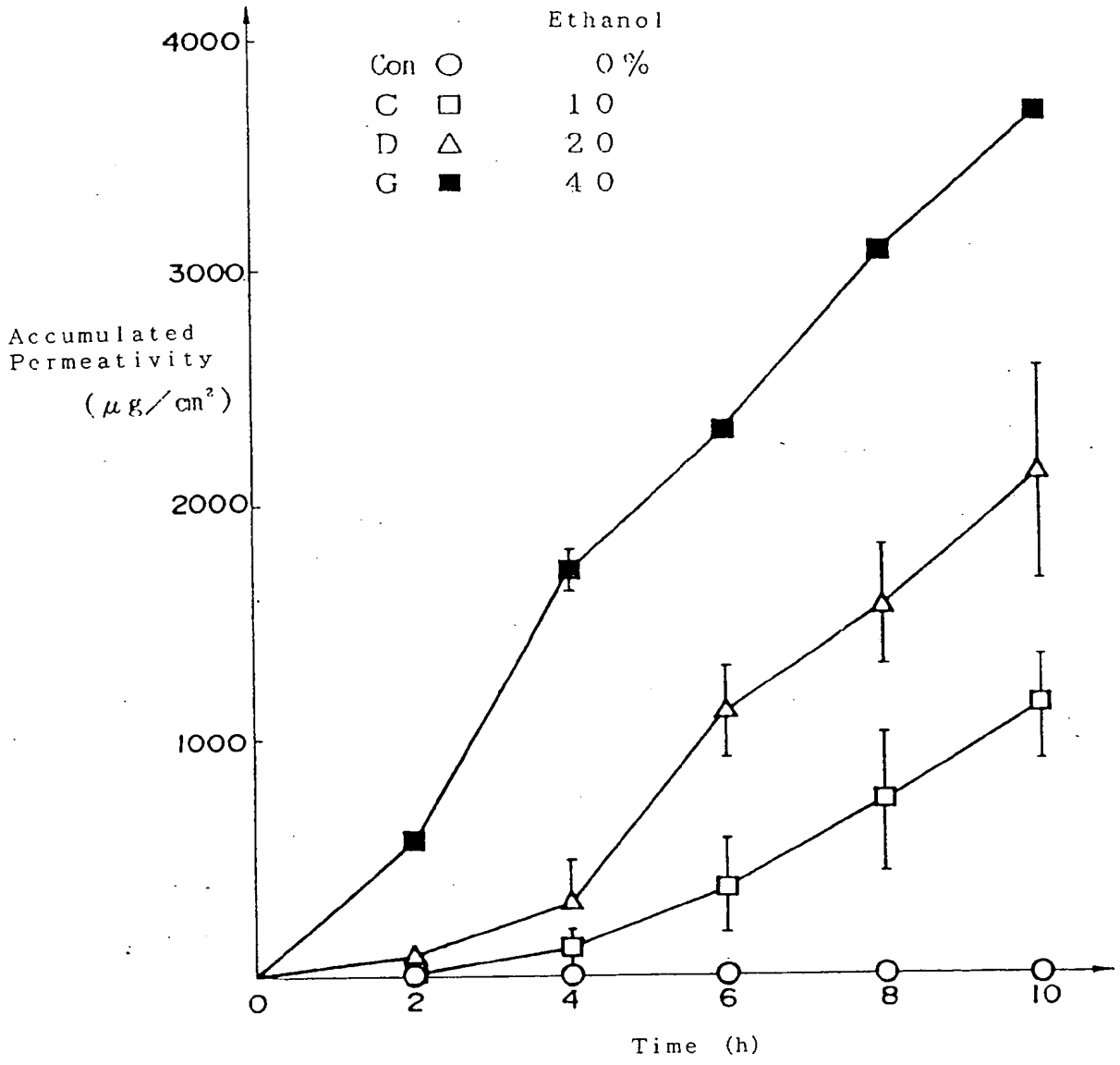
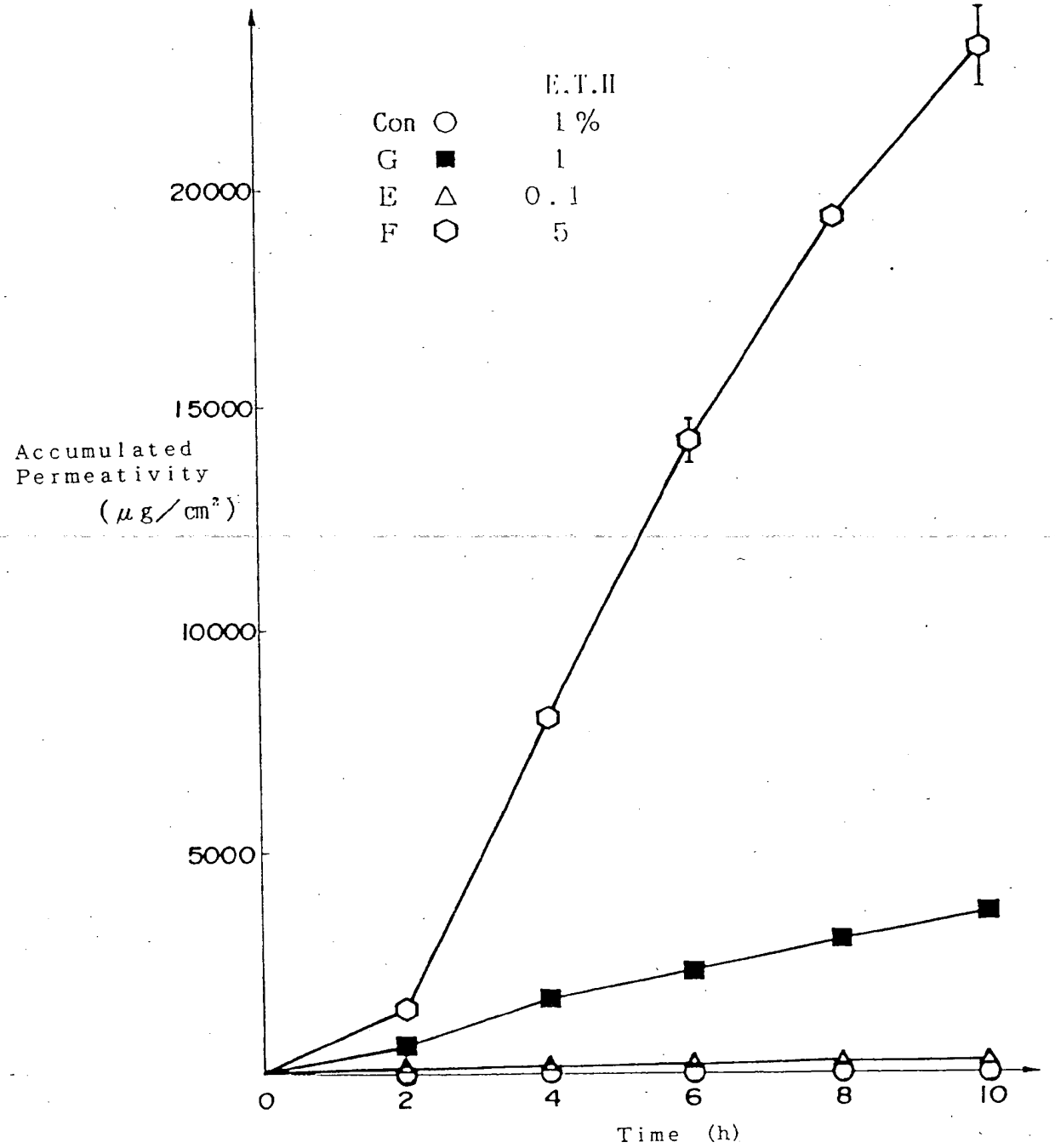


Fig. 11



INTERNATIONAL SEARCH REPORT

International Application No PCT/JP91/00413

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl[5] A61K45/08, A61K31/485, A61K9/08, A61K47/10, A61K47/46, A61K31/55

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	A61K9/08, A61K31/485, A61K45/08

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	JP, A, 57-206610 (Lion Corp.), December 18, 1982 (18. 12. 82), (Family: none)	1-5
X	JP, A, 57-062221 (Lion Corp.), April 15, 1982 (15. 04. 82), (Family: none)	1-5
X	JP, A, 62-033116 (Hisamitsu Pharmaceutical Co., Inc., Nissan Chemical Industries, Ltd.), February 13, 1987 (13. 02. 87)	1-5
Y	JP, A, 61-012614 (Lion Corp.), January 21, 1986 (21. 01. 86), (Family: none)	1-5
A	EP, A, 162239 (KAO CORP.), November 27, 1985 (27. 11. 85), & JP, A, 60-224638 & US, A, 4859696	1-5
Y	JP, A, 56-036411 (Sumitomo Chemical Co., Ltd.),	1-5

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
June 4, 1991 (04. 06. 91)	June 17, 1991 (17. 06. 91)
International Searching Authority	**Signature of Authorized Officer**
Japanese Patent Office	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	April 9, 1981 (09. 04. 81), (Family: none)	
Y	JP, A, 59-139325 (Nissan Chemical Industries, Ltd.), August 10, 1984 (10. 08. 84), (Family: none)	1-5
Y	GB, A, 2203041 (LEAD CHEMICAL CO.), October 12, 1988 (12. 10. 88), & JP, A, 63-227524	1-5
A	DE, A, 2631947 (BAYER AG), January 19, 1978 (19. 01. 78),	1-5

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest

☐ No protest accompanied the payment of additional search fees

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	& BE, A, 856811 & JP, A, 53-012415 & FR, A, 2358162 & GB, A, 1578541, AT, A, 7705134	
Y	EP, A, 171742 (DU PONT DE NEMOURS CO.), February 19, 1986 (19. 02. 86), & AU, A, 8545905 & JP, A, 61-083116 Lower right column, page 8, lower left column, page 9 & US, A, 4626539	1-5

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

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4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

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